Complete Summary

GUIDELINE TITLE

Syphilis. In: Sexually transmitted infections: UK national screening and testing guidelines.

BIBLIOGRAPHIC SOURCE(S)

Lewis DA, Young H. Syphilis. In: Ross J, Ison C, Carder C, Lewis D, Mercey D, Young H. Sexually transmitted infections: UK national screening and testing guidelines. London (UK): British Association for Sexual Health and HIV (BASHH); 2006 Aug. p. 33-9. [13 references]

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Syphilis

GUIDELINE CATEGORY

Diagnosis
Evaluation
Risk Assessment
Screening

CLINICAL SPECIALTY

Family Practice
Infectious Diseases
Internal Medicine
Obstetrics and Gynecology
Urology

INTENDED USERS

Advanced Practice Nurses
Clinical Laboratory Personnel
Nurses
Physician Assistants
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

- To provide advice on what tests for syphilis are most appropriate in a United Kingdom genitourinary (GU) clinic setting (excluding human immunodeficiency virus [HIV]-infected patients)
- To provide a basis for audit
- To support clinics when bidding for additional resources to meet national standards

TARGET POPULATION

Individuals in the United Kingdom with or at risk for syphilis

INTERVENTIONS AND PRACTICES CONSIDERED

1. Syphilis screening for all asymptomatic patients attending a United Kingdom genitourinary (GU) clinic
2. Serological screening tests:
    - *Treponema pallidum* (*T. pallidum*) enzyme immunoassays (EIAs) that detect both immunoglobulin M (IgM) and immunoglobulin G (IgG)
    - *T. pallidum* particle assay (TPPA)
    - *T. pallidum* haemagglutination assay (TPHA) in combination with a cardiolipin antigen/reagin tests
3. Additional and confirmatory serological tests:
    - Enzyme immunoassay (EIA) IgM test in addition to routine screening tests in all cases of genital ulceration as well as in those who are known contacts of syphilis
    - Quantitative TPPA to confirm a positive EIA
    - EIA to confirm a positive TPPA
    - Additional tests such as immunoblotting based on recombinant antigens or the fluorescent antibody absorbed (FTA-abs) test in the case of a discrepancy between the EIA and TPPA
    - EIA for treponemal IgM on all sera reactive in one or more screening tests
    - Quantitative Venereal Disease Research Laboratory/Rapid Plasma Reagin (VDRL/RPR) tests before therapy

4. Direct detection of *T. pallidum* in primary and secondary syphilis using dark ground/dark field microscopy (DGM) or polymerase chain reaction (PCR) testing as appropriate
5. Testing of clotted blood samples for all patients, ulcer material for primary syphilis, and lesion material for secondary syphilis
6. Special considerations for screening of patients who are known contacts of the infection
7. Repeat testing in asymptomatic patients depending on sexual history
8. Test of cure by quantitative VDRL/RPR tests at specified frequencies

MAJOR OUTCOMES CONSIDERED

Sensitivity and specificity of screening tests

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

This guideline was obtained by searching the Medline database from 1965 up until August 2002 using the MeSH headings "syphilis, *Treponema pallidum*, serodiagnosis."

The recommendations of the Public Health Laboratory Service (PHLS) Syphilis Forum, the United Kingdom national guidelines for the management of syphilis, the European guidelines for the management of syphilis and the Centers for Disease Prevention and Control (CDC) sexually transmitted infection (STI) treatment guidelines of 2002 were used as a source for expert consensus.

A key review paper (Young H. Syphilis: new diagnostic directions. Int. J. STD & AIDS 1992;3:391-413) was also consulted.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

Ia: Evidence obtained from meta-analysis of randomised controlled trials

Ib: Evidence obtained from at least one randomised controlled trial

IIa: Evidence obtained from at least one well designed controlled study without randomisation

IIb: Evidence obtained from at least one other type of well designed quasi-experimental study

III: Evidence obtained from well designed non-experimental descriptive studies

IV: Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The guidelines have been developed following the methodological framework of the Appraisal of Guidelines Research and Evaluation instrument (AGREE - adapted as described in *Int J STD and AIDS* 2004 15:297-305).

The extent to which the guideline represents the views of intended users has been addressed primarily by the authorship coming from the multidisciplinary membership of the Bacterial Special Interest Group (BSIG). As practising clinicians the authors were able to draw on their experience of applying the tests to symptomatic and asymptomatic patients, but it was not feasible to obtain formal input from representative patients.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grading of Recommendations

A. Evidence at level Ia or Ib
B. Evidence at level IIa, IIb, or III
C. Evidence at level IV

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

After drafting, other health care professionals and professional bodies in genitourinary (GU) medicine were asked to comment, the draft guidelines posted on the British Association for Sexual Health and HIV (BASHH) website for 3 months, and all comments reviewed before final publication.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Definitions for the level of evidence (**I-IV**) and grade of recommendation (**A-C**) are provided at the end of the "Major Recommendations" field.

Screening for syphilis is recommended for all asymptomatic patients attending a United Kingdom (UK) genitourinary (GU) clinic. There are no controlled studies to support this statement but the recent increase in infectious syphilis in the UK and other European countries supports screening as part of good clinical practice. Apart from the public health benefit of detecting infectious syphilis, screening will detect non-infectious stages of syphilis, which will benefit the individual patient.

Patients with syphilitic lesions will require further investigation as outlined below.

Recommended Tests

Serological Screening Tests

- *Treponema pallidum* (*T. pallidum*) enzyme immunoassay (EIA). (**Evidence Level IIb**; **Grade of Recommendation B**). There are a number of different EIA's to detect anti-treponemal antibodies and very few have been subject to peer review evaluation so it is important to establish satisfactory performance of any EIA used; this applies to all types of serological test.
- EIA's that detect both immunoglobulin G (IgG) and immunoglobulin M (IgM) are recommended as they tend to be more sensitive in primary infection. (**Evidence Level IIb; Grade of Recommendation B**).
- The *T. pallidum* particle assay (TPPA) is recommended in preference to the *T. pallidum* haemagglutination assay (TPHA). (**Evidence Level IV; Grade of Recommendation C**).
- Screening with either EIA alone (**Evidence Level IIb; Grade of Recommendation B**) or the TPPA alone (**Evidence Level IV; Grade of Recommendation C**) is recommended (the TPPA is more sensitive than the TPHA in primary infection).

- The TPHA can be used in combination with a cardiolipin antigen/reagin test such as Venereal Disease Research Laboratory (VDRL) or Rapid Plasma Reagin (RPR) to maximize the detection of primary infection on screening. (**Evidence Level III; Grade of Recommendation B**)

Additional and Confirmatory Serological Tests (Evidence Level IV; Grade of Recommendation C)

- An EIA IgM test should be performed in addition to routine screening tests in all cases of genital ulceration as well as in those who are known contacts of syphilis (see below).

  Note: The rationale for this is that IgM becomes detectable in the serum 2 to 3 weeks after infection and IgG 4 to 5 weeks after infection. Therefore there will be a window of 1 to 2 weeks when routine screening tests may be negative.

- A quantitative TPPA should be used to confirm a positive EIA.
- An EIA should be used to confirm a positive TPPA.
- An additional test such as immunoblotting based on recombinant antigens or the fluorescent antibody absorbed (FTA-abs) test can be used in the case of a discrepancy between the EIA and TPPA.
- An EIA for anti-treponemal IgM should be performed on all sera reactive in one or more of the screening tests.
- Quantitative VDRL/RPR tests should be performed before therapy.

Note: In patients who have previously been treated for syphilis a fourfold increase in VDRL/RPR titre and/or a change in the EIA IgM from negative to positive (confirmed on a second specimen) suggests re-infection or relapse.

Direct Detection of *T. pallidum* in First and Second Degree Syphilis

- Dark ground/dark field microscopy (DGM) of lesion exudate or lymph nodes should be performed by experienced clinicians. (**Evidence Level IV; Grade of Recommendation C**) Because of interference from commensal spirochaetes that are found in the normal flora of the genital and rectal mucosae, DGM is considered to be less reliable in examining rectal and non-penile genital lesions. DGM is not suitable for examining oral lesions.

  Note: To obtain lesion exudates from a presumptive syphilitic chancre for DGM, the ulcer should be cleaned with sterile saline using a gauze swab. Any crust on the ulcer surface should first be removed. The ulcer should then be squeezed for sufficient time to produce sufficient serous fluid to be collected by a loop or other suitable instrument and placed on a glass microscope slide. The exudate should have a coverslip placed over it and DGM performed within 10 minutes in order to look for the characteristic morphology and motility of *T. pallidum* organisms. Other sites from which exudative material can be examined include skin lesions (after removal of the epithelial surface) and condylomata lata. Material from enlarged lymph nodes can be aspirated using a sterile 23 gauge needle and syringe filled with 0.2 ml of sterile saline.

- If the initial examination is negative DGM should be repeated daily for at least three days: antibiotics should be withheld during this period - local saline lavage may be used to reduce local sepsis. (**Evidence Level IV; Grade of Recommendation C**)
- Testing of material submitted on dry swabs by the polymerase chain reaction (PCR) is recommended for oral or other lesions where contamination with

commensal treponemes is likely. (**Evidence Level IV; Grade of Recommendation C**)
- PCR is also useful in the diagnosis of primary syphilis and is available via local laboratories sending samples to the Sexually Transmitted Bacteria Reference Laboratory (STBRL) at the Health Protection Agency (stbrl@hpa.org.uk). (**Evidence Level IV; Grade of Recommendation C**)

Recommended Sites for Testing

- Clotted blood (all patients)
- Ulcer material (primary syphilis)
- Lesion material (secondary syphilis)

Factors Which Alter Tests Recommended or Sites Tested

Genital or extra-genital lesions (including oral) that could be due to primary syphilis or a history of sexual contact with a patient known to have syphilis are the only factors which would influence the recommended tests or sites tested. In these circumstances an anti-treponemal IgM EIA should be performed in addition to the routine tests (see above).

Other aspects of sexual history (e.g., oral sex, unprotected sex with multiple partners, past history of STD, sexual assault) will not alter tests or sites but factors such as unprotected oral, vaginal or anal sex with multiple partners and sexual assault may influence the frequency of repeat testing (see below – "Recommendation for Frequency of Repeat Testing in an Asymptomatic Patient").

Risk Groups

- Men who have sex with men (MSM) (no alteration to standard recommendation)
- Sex workers (no alteration to standard recommendation)
- 'Young' (under 25) patients (no alteration to standard recommendation)

Other

- Pregnant women (no alteration to standard recommendation)
- Women with history of hysterectomy (no alteration to standard recommendation)
- Patients who are known contacts of the infection need a request for an anti-treponemal IgM EIA on the blood specimen submitted for standard screening.

Recommendation for Frequency of Repeat Testing in an Asymptomatic Patient (**Evidence Level IV; Grade of Recommendation C** in each case)

- The frequency of repeat testing depends on the sexual history, particularly type of sexual exposure and number of sexual partners.
- A 'high risk' exposure would include unprotected oral, anal or vaginal intercourse with a 'high risk' partner (e.g., partner with suspected or proven syphilis, homosexual male with multiple partners, anonymous partner(s) in

saunas and other venues, commercial sex worker, partner just arrived from or living in a country where the prevalence of syphilis is known to be high).

- No further testing is recommended if the patient had a single 'low risk' episode more than six weeks previously (this is a pragmatic approach but is based on the scientific premise that the average pre-patent period is three weeks and IgG production starts around the fourth week of infection).
- A repeat screening test is recommended three months after exposure if the patient had a single 'high risk' exposure less than six weeks prior to attending the clinic.
- Routine screening as well as specific EIA-IgM tests should be repeated at six weeks and three months for patients who:
    a. Have had multiple 'high risk' exposures
    b. Have DGM negative ulcerative lesions that could be due to primary syphilis
    c. Are contacts of a suspected or proven case of syphilis, regardless of whether they have received epidemiological treatment for syphilis
- Patients with 'high risk' exposures should be informed about the symptoms of primary or secondary syphilis and encouraged to return immediately if these develop before the next serological screening visit.

Recommendation for Test of Cure

- Quantitative VDRL/RPR tests are recommended (**Evidence Level III; Grade of Recommendation B**) and should be performed with the same antigen (Manufacturer) and in the same laboratory. (**Evidence Level IV; Grade of Recommendation C**)
- VDRL/RPR tests should be performed monthly for three months and at 6 and 12 months for early (infectious) syphilis. (**Evidence Level IV; Grade of Recommendation C**)
- VDRL/RPR tests should be performed every six months until negative/serofast for late (non-infectious) syphilis. (**Evidence Level IV; Grade of Recommendation C**)
- HIV positive patients should have repeat treponemal serology performed yearly, or more frequently if at risk of re-infection with syphilis through their sexual activity (see above – recommendations for frequency of repeat testing). (**Evidence Level IV; Grade of Recommendation C**)
- Lumbar punctures are not normally taken in early syphilis. If lumbar puncture is taken in accordance with appropriate guidelines then the cerebrospinal fluid (CSF) should be tested on a 6 monthly basis until the cell count is normal. (**Evidence Level IV; Grade of Recommendation C**)

<u>Definitions</u>:

Levels of Evidence

Ia: Evidence obtained from meta-analysis of randomised controlled trials

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IIa: Evidence obtained from at least one well designed controlled study without randomisation

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III: Evidence obtained from well designed non-experimental descriptive studies

IV: Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

Grading of Recommendations

A. Evidence at level Ia or Ib
B. Evidence at level IIa, IIb, or III
C. Evidence at level IV

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate screening and diagnosis of syphilis

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- The guideline recommends the use of enzyme immunoassay (EIA) immunoglobulin M (IgM) serological tests and polymerase chain reaction (PCR) testing in certain situations. As these tests are not routinely available, this will impact on laboratory staff as samples, particularly for PCR, will need to be sent away to specialist or reference laboratories capable of performing these tests.
- Staff in genitourinary medicine (GUM) clinics will need to be trained in dark ground/dark field microscopy DGM to increase the sensitivity and the specificity of this test in routine clinical practice.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Audit Criteria/Indicators

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Lewis DA, Young H. Syphilis. In: Ross J, Ison C, Carder C, Lewis D, Mercey D, Young H. Sexually transmitted infections: UK national screening and testing guidelines. London (UK): British Association for Sexual Health and HIV (BASHH); 2006 Aug. p. 33-9. [13 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Aug

GUIDELINE DEVELOPER(S)

British Association for Sexual Health and HIV - Medical Specialty Society

SOURCE(S) OF FUNDING

No specific or external funding was sought or provided in the development of this guideline.

GUIDELINE COMMITTEE

Screening Guidelines Steering Committee
Clinical Effectiveness Group (CEG)

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Authors: David A. Lewis, Department of Genitourinary Medicine, Guy's and St. Thomas' NHS Trust, London; Hugh Young, STD/Chlamydia Laboratory, Department of Laboratory Medicine (Microbiology), Edinburgh Royal Infirmary, Edinburgh

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

David A. Lewis and Hugh Young have no conflicts of interest.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from British Association for Sexual Health and HIV Web Site.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Specifications for the development of UK guidelines on the management of sexually transmitted infections (STIs) and closely related conditions 2005. London (UK): British Association of Sexual Health and HIV (BASHH); 2005. 14 p. Electronic copies: Available in Portable Document Format (PDF) from the British Association for Sexual Health and HIV Web site.

Additionally, auditable outcome measures can be found in the original guideline document.

PATIENT RESOURCES

None available

NGC STATUS

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